Articles

Mycobacterium avium Complex and *Mycobacterium tuberculosis* in Patients Infected With the Human Immunodeficiency Virus

KARLA M. KERLIKOWSKE, MD, *and* MITCHELL H. KATZ, MD, *San Francisco, California*

Primary care physicians play an important role in identifying and treating bacterial infections in adults infected with the human immunodeficiency virus (HIV). *Mycobacterium avium* complex and *Mycobacterium tuberculosis* are pathogens that can cause systemic or local infection in these patients. We review the epidemiology, pathogenesis, clinical presentation, and principles of treatment for these two mycobacterial pathogens. Because *M tuberculosis* disease is preventable and curable and yet communicable, physicians should maintain a high degree of suspicion for tuberculosis in HIV-infected adults. In comparison, the goal of treating *M avium* complex in patients with advanced HIV disease is to reduce constitutional symptoms and improve survival.

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Mycobacterium avium complex and *Mycobacterium tuberculosis* are the most common mycobacteria causing disease in adults infected with the human immunodeficiency virus (HIV). The incidences of infection with these mycobacterial pathogens have steadily increased since the beginning of the HIV epidemic.[1,2] Diagnosing, treating, and preventing these diseases is an increasingly important aspect of caring for HIV-infected patients. We review the epidemiology, pathogenesis, clinical manifestations, and treatment of these two mycobacterial diseases in HIV-infected patients.

Mycobacterium avium Complex

Epidemiology and Pathogenesis

Mycobacterium avium complex accounts for 97% of the nontuberculous mycobacteria identified in patients with the acquired immunodeficiency syndrome (AIDS) and is the most common cause of bacteremia and intrahepatic lesions in patients with AIDS.[3,4] The percentage of AIDS cases in the United States with nontuberculous mycobacteria increased from 5.5% in 1987 to 7.6% in 1990.[1] Clinic-based studies have shown an even higher cumulative incidence of disseminated *M avium* complex, ranging from 18% to 23%. Because disseminated *M avium* complex occurs relatively late in the course of HIV disease, the increased incidence of this infection may be due to the fact that HIV-infected patients are living longer because of better treatment against HIV and opportunistic infections.

The clinical significance of *M avium* complex in HIV-infected patients has been debated. It was initially regarded as a commensal of the gastrointestinal and pulmonary tracts that disseminated in some patients with advanced AIDS but did not contribute to overall mortality. More recent studies have shown that mortality is increased in AIDS patients who have disseminated *M avium* complex. A recent study showed a median survival of 4 months in AIDS patients with disseminated *M avium* complex compared with 11 months in controls without the complex.[5] Moreover, survival when *M avium* complex is the index AIDS diagnosis has been reported to be shorter (median 4.2 months) than when other opportunistic infections such as *Pneumocystis carinii* pneumonia (median 14.7 months) or esophageal candidiasis (median 15.9 months) are the index AIDS diagnosis.[6]

Unlike many of the opportunistic infections that occur in AIDS patients, disseminated *M avium* complex is probably not due to the reactivation of a latent infection.[1] The acquisition of this pathogen appears to result primarily from ingesting water or soil containing *M avium* complex.[7] The pulmonary tract may become infected by aspiration from an infected gastrointestinal tract or possibly by the inhalation of aerosols containing the organism.

It is not known what percentage of patients with localized infection will progress to disseminated disease, nor is it known whether disseminated disease can occur without previous localized infection. Retrospective studies have shown that about 30% to 35% of patients with disseminated disease have infection of the gastrointestinal or pulmonary tracts before dissemination.[8,9] Prospective studies are needed to determine more accurately the relative contribution of respiratory and gastrointestinal tract infection to the dissemination of *M avium* complex.

Clinical Presentation and Diagnosis

Disseminated Mycobacterium avium *complex.* In patients with disseminated *M avium* complex, the diagnosis is made an average of 9 to 12 months from the development of an index AIDS diagnosis.[10,11] About 70% of patients when diagnosed with disseminated disease will have $CD4^+$ lymphocyte counts of less than 50 cells $\times 10^6$ per liter.[12] Only 5% to 6% of patients will have disseminated *M avium* complex as their index AIDS diagnosis. The risk of mycobacterial bacteremia increases each year following an AIDS diagnosis, with *M avium* complex bacteremia developing in about 15% of AIDS patients per year after AIDS has been diagnosed.[13]

Disseminated infections include those cases in which *M avium* complex is cultured from usually sterile tissue—blood, liver, bone marrow, lymph node, cerebrospinal fluid,

From the General Internal Medicine Section, Department of Veterans Affairs Medical Center and the University of California, San Francisco, School of Medicine (Dr Kerlikowske), and the Research Branch, AIDS Office, Department of Public Health, City and County of San Francisco, California (Dr Katz).

Reprint requests to Karla M. Kerlikowske, MD, General Internal Medicine Section (111A1), VA Medical Center, 4150 Clement St, San Francisco, CA 94121.

ABBREVIATIONS USED IN TEXT

AFB = acid-fast bacilli
AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control
HIV = human immunodeficiency virus

pleural fluid, and peritoneal fluid—or, less commonly, from biopsy specimens of disseminated skin lesions. Patients frequently present with constitutional symptoms—fever, weight loss, sweats, anorexia, malaise—and less often with abdominal pain and diarrhea. Hepatosplenomegaly and lymphadenopathy are present in about 50% of patients; anemia (hemoglobin less than 100 grams per liter [10 grams per dl]) and increased alkaline phosphatase activity are also common. Patients with abdominal pain and diarrhea may have intra-abdominal lymphadenopathy. Although these symptoms, signs, and laboratory abnormalities are common in disseminated *M avium* complex, they are not sensitive or specific indicators of disease.

Blood cultures are the most sensitive test to diagnose disseminated *M avium* complex, yielding positive results on average in 14 days (range, 7 to 51 days).[14] In patients with persistent *M avium* complex bacteremia, the first culture is positive 91% of the time; repeating the culture increases the yield to 98%.

There is less information on the diagnostic yield of tissues other than blood when patients do not have mycobacteremia. In a retrospective study of patients who had blood and bone marrow specimens cultured for *M avium* complex, bone marrow biopsies revealed *M avium* complex infection in 26% of cases without isolation of the organism from blood.[15] Culture of liver biopsy specimens in AIDS patients with alkaline phosphatase activity greater than 300 units per liter (normal 30 to 120) and fever of unknown origin has a sensitivity of 75% to 86%. Mycobacteria account for 75% to 85% of the diagnoses made by liver biopsy, and *M avium* complex accounts for 60% to 75% of the total mycobacterial diagnoses.[16] A liver biopsy should be considered for those patients with unexplained fever, blood cultures negative for *M avium* complex, and alkaline phosphatase levels at least two to three times the upper limits of normal.

Localized infections with Mycobacterium avium *complex.* Localized infections (pneumonia, skin nodules, and diarrheal syndromes) tend to occur in HIV-infected patients with better immune function.[3] Pneumonia due to *M avium* complex has no specific radiologic pattern. Localized skin lesions usually occur with lymphadenitis. Patients with gastrointestinal *M avium* complex who present with large-volume diarrhea and steatorrhea often have localized infection in the small intestine; biopsy specimens of the duodenum may show numerous mycobacteria. Patients with gastrointestinal *M avium* complex who present with left lower quadrant pain and small-volume diarrhea usually have infection localized to the colon; rectal biopsy specimens or stool cultures may show numerous mycobacteria.

Principles of Treatment

With recent information on the contribution of *M avium* complex to morbidity and mortality in patients with AIDS, there has been a renewed interest in treating patients with disseminated disease.[17-19] At present, however, the only published studies evaluating the efficacy of the treatment of disseminated *M avium* complex in AIDS patients are uncontrolled, nonrandomized studies. Retrospective studies have shown that patients who are treated with three or more antimycobacterial drugs have improved survival.[5,11] Because treatment regimens varied, however, the optimal treatment regimen to decrease morbidity and prolong survival could not be determined.

Most of the drug regimens currently being given follow the guidelines for the treatment of *M avium* complex infections in patients without AIDS and use at least three to four antimycobacterial drugs for at least 18 to 24 months (Table 1).[17-19] Table 2 lists the drugs currently being used and common side effects from those medications. In addition, there are ongoing clinical trials using macrolides (clarithromycin and azithromycin) as a single agent to treat disseminated *M avium* complex. Studies have shown that administering these macrolides for four to six weeks can reduce *M avium* complex counts in the blood of AIDS patients.[20,21] Whether the long-term administration of macrolides will maintain reduced *M avium* complex counts in the blood and improve survival is not known.

TABLE 1.—*Principles of Treatment of Infection With* Mycobacterium avium *Complex*

Treatment recommended
Documented disseminated *Mycobacterium avium* complex in symptomatic and asymptomatic patients
Lung infiltrate with documentation of *M avium* complex in sputum or bronchoalveolar lavage (BAL) without evidence of other pathogens that could account for the infiltrate
Localized skin nodules with lymphadenitis
Treatment not recommended
Asymptomatic patients with a normal chest x-ray film and *M avium* complex in sputum or BAL
Asymptomatic patients with *M avium* complex recovered from stool
Treatment controversial
Patients with diarrhea who have *M avium* complex cultured from stool or bowel
Treatment guidelines
Begin therapy with a 4-drug oral regimen (ethambutol, rifampin or rifabutin, ciprofloxacin, and clofazimine)
If drug toxicity occurs from 1 or more oral agents, attempt to maintain the patient on at least 3 antimycobacterial drugs
If there is no response to therapy in 4 to 6 weeks, consider adding an aminoglycoside to oral therapy or changing to clarithromycin

Standard mycobacterial sensitivity testing cannot be used to evaluate the susceptibility of these organisms to medication. Minimal inhibitory concentration testing to select antimycobacterial therapy is still investigational and not recommended at this time because methods have not been shown to correlate with the clinical response to therapy.

Efficacy and Prognostic Factors

The best measures of efficacy of antimycobacterial treatment are the resolution of constitutional symptoms and a decreased bacterial burden. With a four-drug oral regimen, about 75% of AIDS patients with disseminated *M avium* complex were asymptomatic at 12 weeks, and about 86% had negative blood cultures.[17] In those patients who respond to treatment, systemic symptoms—fever, sweats, lethargy—usually resolve within four weeks.[19] Treatment has not been found to reverse weight loss or decrease transfusion requirements.

In those institutions where quantitative mycobacterial

TABLE 2.—*Daily Drug Doses for the Treatment of* Mycobacterium avium *Complex**

Drug	*Oral Dose/d*	*Intravenous Dose/d*	*Side Effects*
Ethambutol HCl†	15 mg/kg	--	Decreased visual acuity, abdominal pain, nausea
Rifampin‡	10 mg/kg	10 mg/kg	Rash, nausea, vomiting, hepatitis, thrombocytopenia, renal failure
Ciprofloxacin	750 mg×2	750 mg×2	Abdominal pain, nausea, vomiting, rash, increased creatinine, headache, lightheadedness
Clofazimine	100 mg	--	Skin discoloration, rash, abdominal pain, nausea, vomiting
Amikacin	--	7.5 mg/kg	Nephrotoxicity, ototoxicity
Streptomycin	--	10-15 mg/kg	Ototoxicity, nephrotoxicity
Experimental			
Rifabutin	300-600 mg	--	Diarrhea, nausea, vomiting, rash, leukopenia, hepatitis
Clarithromycin	2,000 mg	--	Hepatitis
Azithromycin	500 mg	--	Diarrhea

HCl = hydrochloride

*From Hoy et al,[17] Chiu et al,[18] Kemper et al,[19] and Dautzenberg.[20]
†Maximum dose, 1,000 mg/d.
‡Maximum dose, 600 mg/d.

blood cultures can be done, decreasing bacterial counts can be used as an indicator of response to treatment. Routine mycobacterial blood cultures are not recommended to monitor response to treatment because the persistence of the organism in cultures does not mean there was not a decrease in bacterial counts.

There is limited information on factors that affect the natural history of disseminated *M avium* complex. Anemia (hematocrit less than 0.25 [25%]) has been reported to be a prognostic indicator of poor survival in patients with disseminated *M avium* complex.[22] Elevated alkaline phosphatase levels are also associated with decreased survival, which may indicate an increased bacterial burden of *M avium* complex in liver and bone marrow.[11]

Surveillance and Prevention

Blood cultures are indicated in HIV-infected patients with signs and symptoms consistent with disseminated *M avium* complex, especially in those patients with $CD4^+$ counts of less than 100 cells $\times 10^6$ per liter. For asymptomatic patients, the diagnostic yield per blood culture is too low to warrant surveillance cultures. In one study done to evaluate the usefulness of screening mycobacterial cultures, about one in five patients tested had a blood culture positive for *M avium* complex. Those with positive blood cultures all had signs or symptoms of disseminated *M avium* complex and $CD4^+$ lymphocyte counts of less than 100 cells $\times 10^6$ per liter.[1,13]

Whether the identification of *M avium* complex in stool or sputum specimens is a predictor of subsequent dissemination is being investigated prospectively. Therefore, screening stool and sputum specimens for *M avium* complex for localized infection in asymptomatic patients is not currently recommended. Trials of primary prophylaxis with clofazimine and rifabutin to prevent disseminated *M avium* complex in patients with low $CD4^+$ lymphocyte counts are ongoing.

In summary, disseminated *M avium* complex is a common infection in patients with advanced HIV disease that causes debilitating symptoms and shortens survival. Because some patients will respond to treatment with a reduction in constitutional symptoms and improved survival, therapy with at least three antimycobacterial agents should be offered to HIV-infected patients with disseminated *M avium* complex.

Mycobacterium tuberculosis

Epidemiology and Pathogenesis

The increased incidence of tuberculosis in the United States in the past five years is primarily due to the HIV epidemic. Tuberculosis is especially common among HIV-infected groups with a recognized high prevalence of *Mycobacterium tuberculosis* infection—African Americans, Hispanics, and injection drug users.[23] Nationally, tuberculosis develops in 4% of AIDS patients[24]; in some urban areas, as many as 28% of patients with tuberculosis are HIV-positive.[25] Based on this observation, HIV testing is recommended for all cases of tuberculosis in areas where there is a high prevalence of HIV infection.[26]

As in immunocompetent adults, 90% of cases of tuberculosis in those infected with HIV are due to a reactivation of latent *M tuberculosis* infection, with 10% of cases due to primary infection. The lifetime risk of tuberculosis developing in tuberculin reactors is at least twofold to threefold greater in HIV-infected patients than in tuberculin reactors who are not HIV-infected, or about a 30% lifetime risk. The rate of conversion to tuberculosis for HIV-infected adults with positive tuberculin reactions is 7% per year for the first two years compared with 0.1% per year for non–HIV-infected adults with a normal chest roentgenogram.[27]

Patients with advanced HIV disease who have had exposure to tuberculosis are at an increased risk for tuberculosis developing compared with persons not infected with HIV.[28] Outbreaks of tuberculosis have been reported in group residences and hospitals that care for patients with advanced HIV disease.[28,29] These observations suggest that recently acquired tuberculous infections can progress rapidly to active disease in patients with advanced HIV disease.

Clinical Presentation and Diagnosis

Most cases of tuberculosis in HIV-infected persons occur before a diagnosis of AIDS has been made. Less than 20% of diagnoses are made after an AIDS diagnosis. Pulmonary disease is the most common manifestation of tuberculosis.

Patients infected with HIV who are not severely immunocompromised usually present with clinically typical pulmonary tuberculosis with apical infiltrates or cavitation on chest roentgenograms. Those who are severely immunocompromised often present with clinically atypical pulmonary and extrapulmonary *M tuberculosis.* Chest roentgenograms of these patients may show hilar or mediastinal adenopathy (or both), middle or lower lobe involvement, diffuse interstitial or miliary disease, or no abnormalities.[26]

Extrapulmonary disease occurs in 50% to 60% of HIV-infected patients with *M tuberculosis* disease, and half of these patients also have pulmonary tuberculosis. Fever and lymphadenitis are the most common presentation of extrapulmonary tuberculosis. Patients with extrapulmonary disease and no evidence of pulmonary involvement tend to have lower mean $CD4^+$ lymphocyte counts (153 cells $\times 10^6$ per liter) than do patients who present with only pulmonary tuberculosis (326 cells $\times 10^6$ per liter).[25]

Evidence of infection with *M tuberculosis* in HIV-infected patients has been defined as 5 mm or greater of induration in reaction to tuberculin antigen.[30] The likelihood of a positive reaction decreases as the length of time after an AIDS diagnosis increases. In one study, patients in whom AIDS developed two years after their episode of pulmonary tuberculosis all had a positive tuberculin reaction (≥ 10 mm of induration) when they were diagnosed with pulmonary tuberculosis. Only 33% of patients who were diagnosed with tuberculosis concurrently with or after their AIDS diagnosis had a positive tuberculin reaction, however.[26] This decrease in tuberculin positivity is thought to be due to depressed cell-mediated responses that occur as $CD4^+$ lymphocyte counts decline. For this reason, some have argued that the cutoff point for infection with *M tuberculosis* should be lowered to 2 mm in patients with HIV infection.[31] At present there are insufficient data on the risk of tuberculosis in HIV-infected adults by tuberculin reaction sizes to make this recommendation.

TABLE 3.—*Treatment Guidelines for Mycobacterium tuberculosis**

Treatment Period	*Oral Dose/d*
First 2 months of therapy.....	Isoniazid, 300 mg Rifampin, 600 mg† Pyrazinamide, 20-30 mg/kg Ethambutol hydrochloride, 25 mg/kg‡
Last 4 to 7 months of therapy or for 6 months after 3 negative cultures	Isoniazid, 300 mg Rifampin, 600 mg

*From the Centers for Disease Control.[26]
†Dose should be 450 mg/d if patient weighs ≤50 kg.
‡Administer when isoniazid resistance is likely.

Although infection with *M tuberculosis* is indicated by a positive tuberculin reaction, isolating *M tuberculosis* from cultures is required to document disease. The sensitivity of acid-fast bacilli (AFB) smears and cultures is the same in HIV-infected patients as in adults not infected with HIV.[25,32] Smears of sputum are positive for AFB 47% to 60% of the time, and cultures are positive 88% to 93% of the time.[25] Cultures of lymph node, bone marrow, and urine also have a high diagnostic yield.

Principles of Treatment

The Centers for Disease Control (CDC) recommendations for the treatment of tuberculosis in HIV-infected patients are listed in Table 3.[26] These guidelines are the same as those for persons not infected with HIV except that a longer period of treatment is recommended. Although the CDC recommends between 9 and 12 months of treatment, retrospective studies suggest that 6 months of treatment is probably as effective as 9 to 12 months. This assumes that the *M tuberculosis* organism isolated is not isoniazid- or rifampin-resistant and that patients can complete two months of therapy with four antimycobacterial drugs and then four months with isoniazid and rifampin for a total of six months of therapy.

Multidrug-resistant tuberculosis has been reported in HIV-infected adults.[33-36] Outbreaks of multidrug-resistant tuberculosis underscore three important points:

- That HIV-infected adults with advanced disease are susceptible to a rapid progression to clinical tuberculosis after infection with *M tuberculosis,*
- That multidrug-resistant tuberculosis has the potential to spread rapidly to health care professionals and persons in group residences with exposure to infectious adults, and
- That drug-susceptibility testing must be done on initial cultures of *M tuberculosis* organisms isolated from all HIV-infected adults.

A high index of suspicion for multidrug-resistant tuberculosis should be maintained, especially when sputum smears remain positive despite therapy for more than three months. In cases of drug resistance, therapy for at least 12 months is recommended and consultation with a specialist is advisable.

Outcome

Sputum conversion occurs at the same rate in HIV-infected patients as in HIV-seronegative patients, with 80% of patients with negative cultures at three months. The reported relapse rate is low at 2% to 5% after six to nine months of therapy.[23] Survival from tuberculosis is decreased in patients with advanced AIDS compared with HIV-infected patients diagnosed with tuberculosis before an index diagnosis of AIDS.[23] The incidence of adverse drug reactions is increased in HIV-infected patients, ranging from 18% to 26%. Patients with AIDS tend to have a higher incidence of drug reactions to antituberculous drugs than HIV-infected patients in whom AIDS has not yet developed.

Prevention

All HIV-infected patients should have a tuberculin skin test and skin test antigens (mumps or tetanus toxoid) applied by the Mantoux method at the time of tuberculin skin testing early in the course of HIV disease. If the initial tuberculin test is negative and the patient is not anergic, the tuberculin skin test should be repeated yearly until either anergy develops or the patient has a positive reaction. If the tuberculin reaction is 5 mm or more of induration, then active disease should be excluded by obtaining a chest roentgenogram and examining peripheral lymph nodes for evidence of infection. In patients who are symptomatic (fever and cough), three sputum specimens for AFB should also be collected. Lymph nodes should be aspirated if signs of infection are present. If active disease is excluded, isoniazid (300 mg) should be administered for 12 months.[30]

Anergic HIV-infected patients with a history of a positive tuberculin test or a chest roentgenogram suggesting previous *M tuberculosis* infection and no history of prophylaxis should be given 12 months of isoniazid therapy after pulmonary and extrapulmonary disease has been excluded. Anergic HIV-infected patients at high risk for *M tuberculosis* infection (injection drug users, prisoners, homeless persons, migrant laborers, and persons born in countries in Asia, Africa, and Latin America) and in whom the tuberculin status is unknown should be considered for preventive therapy.[37,38] Because the recommendations for isoniazid prophylaxis are different for HIV-infected patients, patients with a positive tuberculin reaction whose HIV status is not known should be offered an HIV test if they are from an area of high prevalence of HIV disease.

The efficacy of isoniazid therapy in reducing the incidence of tuberculosis in HIV-infected patients is being evaluated in clinical trials. Data collected in uncontrolled studies suggest that preventive therapy with isoniazid is effective.[27,28] Because HIV-infected patients with tuberculosis respond well to treatment with antimycobacterial drugs, it is assumed that isoniazid prophylaxis will prove to be efficacious when tested in controlled trials.

In summary, tuberculosis is common in HIV-infected patients, and its incidence will probably continue to increase as the prevalence of HIV disease rises. *M tuberculosis* disease is a unique infection in patients with AIDS because it is communicable and virulent and yet preventable and curable. In addition, because tuberculosis can be the first clinical manifestation of cellular immunodeficiency, its recognition allows for HIV testing and staging and the subsequent initiation of antiviral therapy.

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This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the series' editors.

STEPHEN J. McPHEE, MD
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